

**DRAWING AMENDMENTS**

The sheets of drawings submitted herewith include new Figures 5-10. These sheets replace the original sheets including Figures 5-10.

Appendix:                    Replacement sheets (3 sheets, 7 figures)

**REMARKS**

In reviewing this case, applicants wish to amend the elected claims further to include coexpression of Src and Src related proteins. Src related proteins are well known as set forth in the specification at the end of paragraph 8, for example, and include such proteins as Fyn, Yes, Lck, Hck, Lyn, Csk, Blk, etc. Applicants understand that coexpression was included in Group II, former claims 4-6; however, as the Examiner points out, this does not change the issues in examination since it is already recognized in the art by Ikeda, *et al.*, *J. Biol. Chem.* (2002) 277:19206-19212, that coexpression with Src enhances the activity of DDR2 polypeptide. Therefore, this aspect of the invention is not an issue. Applicants respectfully request the indulgence of the Examiner to allow them to prosecute these claims.

In addition to the amendments to claim 16 made for clarity as further discussed below, new claims 24-28 claim essentially the same method but with fewer active steps. Proposed new claims 29-31 are directed to the modified DDR2 kinase domain. This is based on the rationale of the Office that this protein represents a single concept of invention. Therefore, inclusion of these claims is believed proper.

Claims that were formerly not elected have been canceled — *i.e.*, claims 1-15 and 21-22. Claim 19 has been canceled as now redundant.

As further discussed below, claim 16 has been amended in response to the formal rejection under § 112, paragraph 2, and the claim objections as further explained below. Support for the definition of the tyrosine kinase domain is found in paragraph 34 of the specification.

No new matter is added by these amendments and entry of the amendment is respectfully requested.

Priority

A copy of the English language translation of KR10-2003-0076967 along with its Korean language version is enclosed. The number provided to the Office is correct. Applicants believe the Office may have mistaken a publication number for the application number.

Drawings

The meaning of CBB as Coomassie® brilliant blue is set forth in the description of Figure 2 in paragraph 76, and thus, it is believed this designation is clear. This definition applies to all of the figures that contain this designation.

New Figures 5-10 are submitted herewith.

Figure 8 legend in paragraph 82 has been amended to explain the meaning of poly(D<sub>4</sub>Y)<sub>n</sub> – this polymer is obtained from Promega and is a polypeptide wherein a sequence of four aspartic acid residues (symbolized by D) is followed by a tyrosine residue (symbolized by Y) and is repeated multiple times.

In Figure 12, the legend at paragraph 86 of the description now indicates that these images were obtained by P<sup>32</sup> audio radiography (IMG P<sup>32</sup>) by virtue of phosphorylation by P<sup>32</sup> ATP.

Abstract

A new Abstract has been submitted.

Objections to the Specification

It is believed that the minor changes to the specification conform to the enclosed outline. Amendment has already been made to insert (b). The headings (c) and (d) are irrelevant. A Brief Description of the Drawings appears, starting on page 21. Figures 8 and 9 are described in paragraphs 82 and 83; thus there are in fact legends for these drawings.

As the Examiner kindly recognizes, the set of headings is merely suggested and not required.

Claim Objections

Applicants do not understand reference to claims 16-19 previous to the present amendment as reciting non-elected subject matter. Claim 16 has, however, been edited extensively.

The Rejections under 35 U.S.C. § 112, Paragraph 2

Applicants are unclear as to any asserted discrepancy between “DDR2 cytosolic tyrosine kinase” and “DDR2 cytosolic tyrosine kinase domain.” The first phrase is never used absent “domain” at least in the claims as amended.

In claim 16, the comparison standard for the increased activities is now recited. The term “sufficiently” is removed from claim 16 as has the phrase “independently mutated.”

Claim 17 has been amended as suggested by the Office.

It is believed that the amendments to claim 16 avoid the rejection made by the Office. It should be clear that the protein in question must contain positions 441-855 of SEQ ID NO:1 as explained on page 7 of the specification at the end of paragraph 34.

The Rejection under 35 U.S.C. § 112, Paragraph 1

Applicants appreciate the recognition that the specification is enabling at least for making a variant of SEQ ID NO:1 where a phenylalanine is substituted for tyrosine at position 740. The amended claims are somewhat broader than this, but not very much. Reconsideration is respectfully requested based on the amended forms of the claims. As is now made clear, the protein must contain a tyrosine kinase domain represented by positions 441-885 of SEQ ID NO:1. Applicants believe that this is a proper invention scope, since there is a variety of receptors as outlined, for example, in Ellis, *et al.*, cited in connection with the rejection under § 103, where the upstream

portions could be substituted for those of the DDR2 extracellular and membrane bound portions. This allows construction of receptor models that are useful to explore a variety of tyrosine kinase receptor responses. The positions of the tyrosines within the kinase domain have been spelled out in the claims. Thus, the relevant structure of the protein whose tyrosines are to be mutated is clearly spelled out in the amended claims.

As to expansion beyond the substitution of phenylalanine for tyrosine this is predictable to the artisan. Respectfully, alternative substitutions at this position, glycine or alanine, should be equally workable as is understood in the art. Indeed, it is routine to do “alanine scans” where putatively critical amino acids are replaced by alanine. Thus, these alternatives to phenylalanine should not raise questions of enablement. They do not pose an issue as to written description.

As to alternative locations of substitutions, it should be evident from the results described in the specification that a mutation at any one of positions 736, 740 and 741 enhances the tyrosine kinase activity using histone H2B as a substrate as described in paragraph 87, Figure 13 and paragraph 112 in combination. The result with respect to autophosphorylation favors the substitution at position 740 as shown in Figure 12; however, there are positive results at all three positions. All three positions show greater autophosphorylation than the control. It is not necessary to show spectacular results to show that the invention works; it is clear that there is some enhanced phosphorylation at each of these positions. Thus, the application fully supports the scope of the claims as now proposed both with respect to written description and enablement.

#### The Art Rejection

Claims 16-19 were rejected as assertedly obvious over Ellis, *et al.*, *Cell* (1986) 45:721-732, in view of Karn, *et al.*, *Oncogene* (1993) 8:3433-3440.

According to the Office, Ellis, *et al.* teach a method for making an insulin receptor variant having a Tyr<sup>1162</sup>Phe mutation and this variant has increased basal autophosphorylation and kinase activity. Karn is said to teach that Tyr<sup>7410</sup> of human DDR2 kinase is analogous to Tyr<sup>1162</sup> of the insulin receptor.

The teachings of Ellis are somewhat ambiguous in that while the Tyr<sup>1162</sup>Phe variant has increased basal autophosphorylation and kinase activity, this activity is reduced when insulin is supplied. Thus it is thus unclear from Ellis exactly what the effect of this mutation is.

Whatever is taught by Ellis, it is not shown by Karn to be relevant to the present claims. Although the Office states that Karn teaches that Tyr 740 of human DDR2 kinase is analogous to Tyr<sup>1162</sup> of the insulin receptor, and cites Figure 2, Figure 2 does not appear to make any mention of DDR2. Therefore, the teachings of Ellis, whatever they are, are not relevant to the present claims.

Applicants are unable to find any location in Karn that even discusses the human DDR2 receptor, much less its analogy to the insulin receptor. Accordingly, the teachings of the documents when combined, do not predict the results of the invention. Accordingly, this basis for rejection may be withdrawn.

### Conclusion

The claims have been extensively amended to make the invention more precise. It is believed that by virtue of these amendments, the objections under 35 U.S.C. § 112, paragraphs 1 and 2, are overcome. Applicants again respectfully request that the amended claims be examined in this case despite their addition of coexpression with Src or Src related proteins as, by virtue of the art cited by the Examiner (Ikeda, *et al.*) this does not add further complexity to the claims. Finally, the teachings of Ellis are not relevant to the claimed invention since Karn fails to show the

relationship of the positions of tyrosine residues in insulin dependent receptor to positions of tyrosines in the DDR2 receptors of the present case.

In light of the amendments to the claims and the foregoing discussion, applicants believe that claims 16-18, 20 and 23-30 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved by phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket No. 300602005700.

Respectfully submitted,

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